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| <p>(21) International Application Number: PCT/US97/22016</p> <p>(22) International Filing Date: 12 November 1997 (12.11.97)</p> <p>(30) Priority Data: 60/031,741 25 November 1996 (25.11.96) US 08/967,606 10 November 1997 (10.11.97) US</p> <p>(71) Applicant: ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).</p> <p>(72) Inventors: HAMEL, Lawrence, G.; 1215 Arbor Court, Mountain View, CA 94040 (US). AYER, Atul, Devdatt; 931 Bautista Court, Palo Alto, CA 94303 (US). WRIGHT, Jeri, D.; 11305 Rolling Hills Drive, Dublin, CA 94568 (US). LAM, Andrew; 1506 38th Avenue, San Francisco, CA 94122 (US). SHIVANAND, Padmaja; 870 E. El Camino Real #44, Mountain View, CA 94040 (US).</p> <p>(74) Agents: SABATINE, Paul, L. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).</p> | | <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <p>(54) Title: ASCENDING-DOSE DOSAGE FORM</p> | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <table border="1"> <caption>Data points for Release Rate vs Time</caption> <thead> <tr> <th>Time (Hours)</th> <th>Release Rate (mg/hr)</th> </tr> </thead> <tbody> <tr><td>0</td><td>0.0</td></tr> <tr><td>0.5</td><td>0.2</td></tr> <tr><td>1.5</td><td>0.7</td></tr> <tr><td>2.5</td><td>1.1</td></tr> <tr><td>3.5</td><td>1.4</td></tr> <tr><td>4.5</td><td>1.8</td></tr> <tr><td>5.5</td><td>2.2</td></tr> <tr><td>6.5</td><td>2.5</td></tr> <tr><td>7.5</td><td>2.1</td></tr> <tr><td>8.5</td><td>1.5</td></tr> <tr><td>9.5</td><td>1.0</td></tr> <tr><td>10.5</td><td>0.6</td></tr> <tr><td>11.5</td><td>0.4</td></tr> </tbody> </table> | | | Time (Hours) | Release Rate (mg/hr) | 0 | 0.0 | 0.5 | 0.2 | 1.5 | 0.7 | 2.5 | 1.1 | 3.5 | 1.4 | 4.5 | 1.8 | 5.5 | 2.2 | 6.5 | 2.5 | 7.5 | 2.1 | 8.5 | 1.5 | 9.5 | 1.0 | 10.5 | 0.6 | 11.5 | 0.4 |
| Time (Hours) | Release Rate (mg/hr) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| 0.5 | 0.2 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1.5 | 0.7 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 2.5 | 1.1 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 3.5 | 1.4 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 4.5 | 1.8 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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| 8.5 | 1.5 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 9.5 | 1.0 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 10.5 | 0.6 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 11.5 | 0.4 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| <p>(57) Abstract</p> <p>A dosage form and a method are disclosed for delivering to a human patient a drug in an ascending amount over time.</p> | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

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ASCENDING-DOSE DOSAGE FORM

FIELD OF THE INVENTION

This invention relates to a dosage form for delivering an increasing dose of drug. The invention concerns further a dosage form for delivering an increasing dose of drug per unit time over an extended time for continuous effective therapy. The invention pertains additionally to a novel longitudinal dosage form comprising a lengthwise dimension greater than its diameter-wise dimension for delivering an increased dose of drug over a sustained period of therapy. The invention concerns further a method for delivering a dose of drug from the dosage form provided by this invention in an ascending dose for a known therapeutic purpose.

BACKGROUND OF THE INVENTION

For a long time, from antiquity to the present, pharmacy and medicine in all societies used medicines as chemotherapeutics, cancer chemotherapeutics, antiviral therapeutics, for treating neurological maladies, as immunosuppressive drugs, for pain relief, for managing mood, thought, feeling, behavior, psychological personality and pharmacological benefits. The medicines used in these therapies are represented by analgesics, antineoplastics, cytoprotectives, vasomodifiers, opioids, barbiturates, hypnotics, central nervous system stimulants, psychostimulants, psychodepressants, alcohols, cannabinoids, catecholamines, and therapies known in the United States Pharmacopeia, 1997 Ed. While these medicines or therapies have a benefit, a serious problem, called tolerance, is associated with their use. The development of tolerance to a drug results from adaptive changes within the affected patient, such that the therapeutic response is reduced in the presence of the same dose of drug. Tolerance to some drugs, for example, to opioids, is characterized by a shortened duration and decreased intensity of the therapeutic effect. Most of the tolerance seen with

1 many drugs is due to adaptation of cells in the nervous system to the drug's in
2 vivo action, as noted in The Pharmacological Basis of Therapeutics,
3 Goodman and Gilman, 7th Ed., p. 534 (1940).

4 In the broad practice of medicine to which this invention is relevant,
5 one class of these drugs that has become the standard intervention for the
6 management of behavior and personality, including attention deficit disorders,
7 is the central nervous system stimulants. While this invention presents the
8 central nervous system acting drugs in detail, it is understood the invention is
9 generic and it embraces drugs broadly as administered by the dosage form,
10 and the mode and the manner of this invention.

11 The benefits perceived by health-care providers, physicians,
12 psychiatrists, psychologists, social workers, and clinicians are dramatic for
13 central nervous system drugs, and this has resulted in the widespread and
14 accepted use of the central nervous system acting drugs to treat attention
15 deficit disorder. In the latest period for collecting data, 1996, it was observed
16 that about two percent of the school-aged female population and about six
17 percent of the school-aged male population, for a total of about two million
18 patients, were administered medication for attention deficit disorder.

19 Prior to this invention, drugs including opioids, barbiturates, hypnotics,
20 central nervous system stimulants, central nervous system depressants,
21 psychostimulants, alcohols, cannabinoids, catecholamines and other drugs
22 were administered by a standard pharmaceutical dosage form. For example,
23 one prior art dosage form for administering a drug consists in using an
24 immediate release tablet containing the drug. This immediate release form
25 delivers the drug by instant dumping of the drug and produces uneven blood
26 levels characterized by peaks and valleys. For an immediate-release dosage
27 form containing a drug that has a rapid onset and a short half-life, this drug
28 may need multiple doses each day and this can result in swings in blood
29 levels as the medication loses its therapeutic effect. This type of dosage
30 form does not provide the needed therapy over an extended time.

1 Another prior art dosage form for dispensing a drug is the sustained-
2 release dosage form. The sustained-release dosage form delivers a drug in
3 a nonascending profile, often in a descending profile, over time. This dosage
4 form, however, may not provide the required therapy and the appropriate
5 blood pattern. For drugs, such as the central nervous system acting drugs,
6 that are delivered from a sustained-release, nonascending dosage form,
7 the patient often develops an acute tolerance to the drug which is manifested
8 by a short duration and a decrease in the intensity needed for acceptable
9 therapy. The prior art sustained-release dosage form is devoid of means
10 that compensate for its shortcomings inherent therein.

11 The above presentation teaches that a critical and pressing need
12 exists for a novel dosage form for delivering a drug that overcomes the
13 shortcomings known to the prior art. That is, a long-felt need exists for a
14 dosage form for (1) delivering a drug in a sustained-ascending rate that
15 simultaneously reduces or eliminates the need for frequency of daily dosing;
16 for (2) delivering a drug in a sustained-compensating dose to substantially
17 compensate for acute tolerance to the drug and thereby maintain a
18 preselected clinical profile; for (3) administering the drug in an increasing
19 dose to lessen or eliminate acute or chronic tolerance to the drug to provide
20 effective therapy; and (4) for delivering the drug in a sustained, ascending-
21 controlled profile clinically indicated for both medical and psychomedical
22 effects.

23 24 OBJECTS OF THE INVENTION

25
26 Accordingly, in view of the above presentation, it is an immediate
27 object of this invention to provide a novel and unique dosage form that
28 overcomes the shortcomings known to the prior art and thereby makes an
29 advancement in the drug dispensing art.

1 Another object of the invention is to make available to the medical
2 and mental health arts a novel and unique dosage form that provides an
3 ascending dose of drug over a sustained time.

4 Another object of the invention is to provide a dosage form for
5 maintaining the therapeutic effect of a drug in a patient that acquires a
6 tolerance to the drug, wherein the dosage form comprises a dose of drug
7 that is released in an ascending dose to a patient that acquired tolerance
8 to the drug to lessen the effect of tolerance and concomitantly provide the
9 intended therapy.

10 Another object of the invention is to provide a dosage form for
11 maintaining the therapeutic effect of a drug in a patient that acquired acute
12 tolerance to the drug, wherein the dosage form is designed and shaped as a
13 tablet for oral administration and delivers to a patient the drug in a dosage
14 form controlled, increasing dose to compensate for the acute tolerance
15 associated with this drug.

16 Another object of the invention is to provide a dosage form designed
17 and shaped as an osmotic tablet for oral administration into the
18 gastrointestinal tract, comprising a dose of drug for administering to a patient
19 that acquires chronic tolerance to the drug, for administering the drug in a
20 controlled increasing dose, to provide drug compensation for the acquired
21 chronic tolerance associated with the drug.

22 Another object of the invention is to make available a dosage form
23 comprising a length greater than its thickness for lessening the incidence of
24 acquired tolerance in a patient, wherein the dosage form is characterized by
25 administering the drug in a sustained and increasing dose over time to
26 produce the intended therapeutic effect.

27 Another object of the invention is to provide a dosage form
28 manufactured as a longitudinal tablet possessing a lengthwise dimension in
29 excess of its diameter-wise dimension for administering a drug selected from
30 the group consisting of an opioid, barbiturate, hypnotic, central nervous
31 system stimulant, central nervous system depressant, psychostimulant,

1 cannabinoid and catecholamine in a controlled, changing dose that
2 overcomes the shortcomings known to the prior art.

3 Another object of the invention is to make available a method for
4 lessening the incidence of acquired tolerance in a patient administered a
5 drug that develops tolerance in the patient, wherein the method comprises
6 an improvement by administering a dosage form manufactured initially as a
7 compressed tablet that in operation in a fluid environment dispenses a drug
8 in a sustained and increasing dose to substantially lessen the unwanted
9 effects of tolerance and to produce the intended therapy over four hours to
10 thirty hours.

11 Another object of the invention is to make available a dosage form,
12 designed as an oral pharmaceutically acceptable tablet, comprising a first
13 layer of drug and a second layer that pushes the first layer from the tablet,
14 to provide a sustained and ascending dose of drug.

15 Another object of the present invention is to make available a method
16 for administering a drug in a sustained and increasing dose by administering
17 an osmotic dosage tablet comprising a drug composition that delivers the
18 drug in an initial concentration, followed by a second, higher concentration
19 from the original drug composition to effect a sustained and ascending dose
20 of drug.

21 Another object of the invention is to make available a dosage form
22 manufactured as an osmotic tablet comprising a single composition
23 containing a drug administered in a sustained and ascending dose profile
24 over time.

25 Another object of the invention is to make available a dosage form
26 manufactured as an osmotic tablet comprising an immediate-release dose of
27 drug on the exterior of the osmotic tablet, and a prolonged-ascending dose in
28 the interior of the osmotic tablet, which exterior and interior doses operate
29 successively to provide an ascending dose of drug to negate acquired and
30 developed tolerance.

1 Another object of this invention is to make available a dosage form
2 manufactured as an osmotic oral tablet comprising an immediate dose of drug
3 on the exterior of the osmotic tablet, and an interior bilaminate comprising a
4 drug laminate comprising a dose of drug, and an expandable laminate
5 comprising an expandable hydrogel, which osmotic tablet in operation
6 delivers a dose of drug immediately in up to one hour from the exterior of
7 the osmotic tablet, and a dose of drug in from fifteen minutes up to twenty-
8 four hours from the interior of the osmotic tablet by the expandable laminate
9 pushing the interior drug from the osmotic tablet, whereby through the
10 combined operations of the exterior dose, the interior laminate, and the
11 expandable laminate, the osmotic tablet provides an ascending dose of
12 drug for therapy over time.

13 These objects, as well as other objects, features and advantages of
14 this invention will become more apparent from the following detailed
15 disclosure of the invention accompanied by the accompanying claims.

16

17 BRIEF DESCRIPTION OF THE DRAWING FIGURES

18

19 Figure 1 illustrates an ascending release rate profile for a dosage
20 form comprising the drug pseudoephedrine hydrochloride as provided by
21 the invention;

22 Figure 2 depicts an ascending-increasing dose release rate for a
23 dosage form of the invention comprising the central nervous system
24 stimulating drug methylphenidate hydrochloride; and,

25 Figure 3, depicts the release rate in mg/hr for methylphenidate from a
26 dosage form provided by the invention.

27

28 DETAILED DESCRIPTION OF SPECIFICATION

29

30 In accordance with the practice of this invention, it has now been
31 discovered a novel dosage form can be made available characterized by an

1 ascending rate of drug delivery over time. The dosage form provided by this
2 invention delivers a drug at a continuously increasing rate for a predetermined
3 period of time. The dosage form of this invention is unexpected and it is a
4 breakaway from the prior art existing dosage form technologies that deliver
5 a drug at a constant zero-order unchanging rate over time. The dosage form
6 of this invention avoids delivery at a zero order rate as it delivers a drug
7 continuously in an ascending rate over time. The profile of the prior art
8 dosage form consists of a short start-up in delivery, followed by a constant
9 unchanged rate. The profile of this invention departs from the prior art by
10 making available a dosage form wherein the drug release rate follows an
11 ascending profile to achieve a desired drug delivery pattern. The dosage
12 form of this invention achieves the ascending pattern by combining the
13 dimensions of the dosage form with the internal formulation of the dosage
14 form.

15 The dosage form of this invention comprises a wall that surrounds
16 an internal compartment. The wall of the dosage form comprises a
17 semipermeable composition permeable to the passage of fluid present in
18 an environment of use, such as the aqueous biological fluid of the
19 gastrointestinal tract, and the wall is impermeable to the passage of drug.
20 The wall maintains its physical and chemical integrity during the drug
21 dispensing life of the dosage form. The semipermeable wall comprises a
22 polymer selected from the poly(cellulose) group consisting of cellulose
23 acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose
24 diacetate and cellulose triacetate. The wall comprises 100 wt% (weight
25 percent) of said poly(cellulosic) polymer possessing a number-average
26 molecular weight of 15,000 to 4,000,000. The wall, in another manufacture,
27 can comprise from 40 wt% to 100 wt% of the poly(cellulosic) polymer and
28 from 0 to 35 wt% of a hydroxypropylalkylcellulose selected from the group
29 consisting of hydroxypropylmethylcellulose, hydroxypropylethylcellulose,
30 hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose of 9,000 to
31 240,000 number-average molecular weight; 0 to 25 wt% of a

1 hydroxyalkylcellulose comprising a member selected from the group
2 consisting of hydroxymethylcellulose, hydroxyethylcellulose,
3 hydroxypropylcellulose, and hydroxybutylcellulose of 7,500 to 200,000
4 number-average molecular weight; and 0 to 25 wt% of poly(ethylene glycol)
5 of 190 to 40,000 intrinsic viscosity molecular weight. The total weight of all
6 components comprising the wall is equal to 100 wt%. Wall-forming polymers
7 are known in U.S. Patent Nos. 3,845,770; 3,916,899; 4,036,228; 4,111,202;
8 and 5,178,866.

9 The dosage form comprises one or more than one exit in the wall that
10 connects the exterior of the dosage form with the interior of the dosage form.
11 The term "exit" as used herein comprises a passageway, orifice, pore,
12 micropore, micro-opening, hollow fiber, capillary tube, porous overlay, porous
13 insert, and osmotic opening for dispensing a drug from the dosage form.

14 The exit passageway embraces further a material that erodes, or is leached
15 from the wall in a fluid environment of use, such as the gastrointestinal tract.
16 Representative materials for forming an erodible passageway include erodible
17 poly(glycolic) acid, erodible poly(lactic acid), erodible poly(orthoester),
18 erodible poly(orthocarbonate), erodible poly(acetal), a gelatinous filament,
19 poly(vinyl alcohol), leachable materials including fluid removable pore-forming
20 polysaccharides, salts, sugars and oxides. An exit can be formed by leaching
21 compounds such as sorbitol, lactose or glucose. The exit can have any
22 operative shape such as round, triangular, square, or elliptical. The dosage
23 form can be provided with one or more passageways close together or in
24 spaced apart positions on a common surface of the dosage form.

25 Passageways and equipment for forming an exit are disclosed in U.S.
26 Patent Nos. 3,845,770; 3,916,899; 4,063,064; 4,088,864; 4,200,098;
27 4,285,987; and 5,178,866.

28 The dosage form comprises internally a first drug layer and a second
29 expandable layer. The first layer is next to the exit to provide for drug delivery
30 from the dosage form. The first layer comprises a dose of 240 ng
31 (nanograms) to 700 mg (milligrams) of drug, and from 1 mg to 200 mg of a

1 pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier
2 comprises a hydrophilic polymer selected from the group consisting of a
3 poly(alkylene oxide) of 25,000 to 1,000,000 number-average molecular
4 weight where a 5% aqueous solution exhibits a viscosity at 25°C of 12 to
5 17,600 cps (centipoise) represented by a member selected from the group
6 consisting of poly(methylene oxide), poly(ethylene oxide), poly(propylene
7 oxide), poly(butylene oxide), copolymer poly(ethylene oxide)-poly(propylene
8 oxide); and a blend of two different poly(alkylene oxides), such as a
9 poly(alkylene oxide) of 40,000 to 500,000 molecular weight with a different
10 poly(alkylene oxide) of 40,000 to 500,000 molecular weight, a poly(ethylene
11 oxide) of 100,000 molecular weight with a poly(ethylene oxide) of 200,000
12 molecular weight, or a poly(ethylene oxide) of 200,000 molecular weight with
13 a poly(ethylene oxide) of 300,000 molecular weight, which poly(alkylene
14 oxide) polymers are available from Union Carbide Corp.; 0 mg to 200 mg
15 of a pharmaceutical excipient such as starch, talc, mannitol, sorbitol, glucose,
16 fructose, polysaccharides or silicon dioxide; 0 mg to 125 mg of a hydrophilic
17 pharmaceutically acceptable carboxyvinylpolymer, also known as
18 carboxypolyalkylene polymer, possessing a 7,500 to 1,000,000 number-
19 average molecular weight, including a carboxyvinylpolymer of 450,000
20 number-average molecular weight, a carboxyvinylpolymer of 750,000
21 number-average molecular weight, a carboxyvinylpolymer of 1,250,000
22 number-average molecular weight, and a carboxyvinylpolymer of
23 3,000,000 number-average molecular weight, as disclosed in U.S.
24 Patent Nos. 2,798,053; 2,909,462; and 3,825,068, and available as
25 Carbopol® polymer from B.F. Goodrich Company; and 0 mg to 250 mg
26 of a pharmaceutically acceptable alkali carboxyalkylcellulose, wherein the
27 alkali is sodium or potassium represented by sodium carboxymethylcellulose
28 of 10,000 to 7,000,000 viscosity-average number molecular weight, available
29 from the Hercules Corporation; a surfactant selected from 0.0 mg to 7.5 mg
30 of a member selected from the group consisting of amphoteric, anionic,
31 cationic, and nonionic surfactants, as represented by sorbitan trioleate,

1 sorbitan tristearate, ethylene glycol fatty acid ester, polyethylene glycol
2 monostearate, sorbitan sesquioleate, glycerol monostearate, sorbitan
3 monooleate, propylene glycol monolaurate, sorbitan monostearate, diethylene
4 glycol monolaurate, sorbitan monopalmitate, polyoxyethylene mannitol
5 dioleate, sorbitan monolaurate, polyoxyethylene lauryl ether, polyoxyethylene
6 monostearate, polyethylene glycol 400 monostearate, triethanolamine oleate,
7 polyoxyethylene alkyl phenol, polyethylene alkyl aryl ether, polyoxyethylene
8 sorbitan monolaurate, polyoxyethylene sorbitan monostearate,
9 polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan
10 monopalmitate, polyoxyethylene monostearate, polyoxyethylene sorbitan
11 monolaurate, polyoxyethylene lauryl ether, sodium oleate, and sodium
12 lauryl sulfate, which surfactants are known in Pharmaceutical Sciences,
13 Remington, 17th Ed., pp. 1305-1306 (1985); 0 mg to 20 mg of a
14 hydroxypropylalkylcellulose binder selected from the group consisting
15 of hydroxypropylmethylcellulose, hydroxypropylethylcellulose,
16 hydroxypropylbutylcellulose and hydroxypropylpentylcellulose of 9,000
17 to 750,000 number-average molecular weight, available from the Dow
18 Chemical Company, and a polyvinylpyrrolidone binder of 7,500 to 350,000
19 molecular weight; and 0.0 mg to 20 mg of a hydroxyalkylcellulose selected
20 from the group consisting of hydroxymethylcellulose, hydroxyethylcellulose,
21 hydroxypropylcellulose, hydroxybutylcellulose and hydroxypentylcellulose of
22 7,500 to 750,000 weight-average molecular weight, available from Aqualon
23 Company; and 0.01 mg to 5 mg of a lubricant such as stearic acid,
24 magnesium stearate, calcium stearate, potassium oleate, magnesium
25 laureate and calcium palmitate. The expression "pharmaceutically
26 acceptable" as used herein means the polymer, compound or drug denotes
27 nontoxic and is acceptable for oral administration to a human patient.

28 The dosage form comprises a second layer that displaces or pushes
29 the first drug layer through the exit port from the dosage form. The second
30 layer comprises 100 ng to 400 mg of a hydrophilic osmopolymer selected
31 from the group consisting of a poly(alkylene oxide) of 1,500,000 to

1 10,000,000 number-average molecular weight; or an alkali
2 carboxyalkylcellulose of 1,750,000 to 10,000,000 of viscosity-average
3 number molecular weight; 0 to 100 mg of a hydroxypropylalkylcellulose
4 comprising hydroxypropylmethylcellulose, hydroxypropylethylcellulose,
5 hydroxypropylbutylcellulose and hydroxypropylpentylcellulose of 9,000 to
6 750,000 number-average molecular weight; 0 to 400 mg, generally 25 mg
7 to 400 mg, of a hydroxyalkylcellulose selected from hydroxymethylcellulose,
8 hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose of
9 7,500 to 1,500,000 number-average molecular weight; from 0 to 250 mg,
10 with a present manufacture of 10 mg to 175 mg, of an osmagent, also known
11 as osmotically effective solute, osmotically effective compound, and osmotic
12 agent, including inorganic and organic compounds, selected from the group
13 consisting of magnesium sulfate, magnesium chloride, sodium chloride,
14 lithium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium
15 chloride, sodium sulfate, magnesium succinate, tartaric acid; carbohydrates
16 such as raffinose, sucrose, glucose and lactose; from 0.001 mg to 10 mg of a
17 surfactant selected from the group consisting of amphoteric, anionic, cationic
18 and nonionic surfactants, present in the first drug layer; 0 mg to 20 mg of a
19 carboxyvinylpolymer of 7,500 to 10,000 number-average molecular weight,
20 present in the first drug layer; 0 mg to 5 mg of a colorant compound to identify
21 the dosage form, such as red ferric oxide or black ferric oxide; and 0 mg to
22 5 mg of a lubricant including the lubricants presented in the first drug layer.

23 The dosage form provided by this invention is designed and shaped
24 as a dosage form tablet. The dosage form tablet comprises a length greater
25 than its width individually. The dosage form tablet comprises a length of
26 5 mm to 28 mm, and a width of 2.50 mm to 10 mm. The dosage form tablet
27 provided by this invention comprises in the second layer 60% to 95% of
28 osmopolymer, or 60% to 95% of a combination comprising an osmopolymer
29 and an osmagent. The high percent of osmopolymer, or high percent
30 osmopolymer and osmagent composition, joined with the dimensions of the

1 dosage form tablet, enables the dosage form tablet to make available an
2 ascending delivery of drug for 2 hours to 24 hours.

3 Representative of a drug present in the drug layer comprises a drug
4 composition comprising an opioid, barbiturate, hypnotic, central nervous
5 system acting drug, psychostimulant, psychodepressant, analgesic, alcohol,
6 cannabinoid, and catecholamine. Examples of drugs are central nervous
7 system acting drugs for the management of attention deficit disorder,
8 including catecholamines and drugs that can mimic their action. The drugs
9 for this therapy comprise a member selected from the group consisting of
10 amphetamine, dextroamphetamine, methamphetamine, methylphenidate,
11 racemic methylphenidate, threomethylphenidate, ethylphenidate,
12 phenylisopropylamine and pemoline. The drugs include racemates,
13 stereoisomers and enantiomers of a racemic drug. The drugs include their
14 pharmaceutically acceptable salts, such as a member selected from the
15 group consisting of hydrochloride, fumarate, sulfate, phosphate, lactate,
16 malate, acetate, tartrate, hydrobromide, citrate, pamoate, maleate, ascorbate,
17 gluconate, aspartate, and salicylate.

18 The invention comprises further, on the external surface of the dosage
19 form, a coat composition comprising a drug. The coat composition is an
20 external overcoat carried by the dosage form. The external overcoat on the
21 wall of the dosage form comprises a dose of drug, and the overcoat
22 cooperates with the interior compartment comprising a dose of drug that
23 delivers the drug, to provide an initial unexpected ascending drug delivery
24 profile. The overcoat provides an initial dose of drug followed by a dose of
25 drug from the interior of the dosage form to give an ascending drug delivery
26 profile. The overcoat comprises 10 ng to 100 mg of a drug that is delivered in
27 up to one hour, followed by the dose from the dosage form. The dose of drug
28 from the interior is delivered over 24 hours. The overcoat comprises a drug
29 selected from the group consisting of opioids, barbiturates, hypnotics,
30 psychostimulants, psychodepressants, central nervous system acting drugs,
31 analgesics and catecholamines. Representative of individual drugs present in

1 the overcoat comprise a drug selected from the group consisting of
2 amphetamine, dextroamphetamine, methamphetamine, methylphenidate,
3 racemic methylphenidate, threomethylphenidate, ethylphenidate,
4 alkylphenidate, phenylisopropylamine, and pemoline. These drugs include
5 their pharmaceutically acceptable salts such as a member selected from the
6 group consisting of hydrochloride, sulfate, phosphate, acetate, hydrobromide,
7 pamoate, malate, maleate, fumarate, ascorbate, tartrate and citrate.
8 Representative of a drug embodiment present in the overcoat is an
9 alkylphenidate comprising 10 ng to 25 mg of methylphenidate.

10 The overcoat comprises the drug blended with a pharmaceutically
11 acceptable carrier. The pharmaceutically acceptable carrier comprises an
12 aqueous, drug-releasing carrier selected from the group consisting of an
13 alkylcellulose, methylcellulose, ethylcellulose, hydroxyalkylcellulose,
14 hydroxymethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose,
15 hydroxybutylcellulose, hydroxypropylalkylcellulose,
16 hydroxypropylmethylcellulose, hydroxypropylethylcellulose,
17 hydroxypropylbutylcellulose, methyl dextrose, acacia, guar gum,
18 pregelatinized starch, propylene glycol alginate and cyclodextrin.

19 The overcoat comprises 0.01 wt% to 15 wt% of the pharmaceutically
20 acceptable carrier. The dosage form overcoat in another manufacture
21 comprises 0.01 wt% to 5 wt% of a member selected from the group
22 consisting of polyethylene glycol, polypropylene glycol, polyvinylpyrrolidone,
23 and acetylated triglycerides. The overcoat provides needed drug therapy,
24 for example, methylphenidate, as the overcoat dissolves or undergoes
25 dissolution in the presence of fluid present in the gastrointestinal tract of a
26 patient. Thus, the overcoat provides drug therapy on oral administration into
27 the patient's drug receiving environment, the gastrointestinal tract, for an
28 immediate therapeutic benefit.

29 The wall of the dosage form in one manufacture is formed by an air-
30 suspension procedure. This procedure consists of suspending and tumbling
31 compressed bilayer cores in a current of air and wall-forming composition until

1 a wall is applied forming and surrounding an internal compartment containing
2 the bilayer core. The air-suspension procedure is well suited for forming the
3 wall. The air-suspension procedure is described in U.S. Patent Nos.
4 2,799,241 and 5,082,668. The wall can be formed in an air-suspension
5 coater using cosolvents. Representative cosolvents are: methylene
6 dichloride-methanol, 80:20 wt:wt; or acetone-water cosolvent 85:15, or 90:10,
7 or 95:5, or 99:1 wt:wt, using 1% to 7% solids. Other wall-forming techniques
8 can be used, such as a pan coating system, or a wall forming composition
9 deposited by successive spraying of the composition accompanied by
10 tumbling in a rotating pan. A pan coater may be used to produce thicker
11 walls. A large volume of solvent can be used in a solvent system to produce
12 a thinner wall. Finally, the wall-coated compartment is dried in an oven at
13 30°C to 50°C for up to a week, or in a humidity controlled oven at 50 RH
14 (relative humidity) and 50°C for 18 hours to 3 days.

15 The first and second layers of the invention are made by standard
16 manufacturing techniques. For example, in one manufacture the drug and
17 other ingredients are blended and pressed into a solid layer. The drug and
18 the ingredients can be blended with a solvent and mixed into a semisolid or
19 solid formed by conventional methods such as ball-milling, calendering,
20 stirring or roller milling, and then pressed into a preselected shape. The first
21 layer possesses dimensions that correspond to the internal dimensions of the
22 area the layer occupies in the dosage form. It also possesses dimensions
23 corresponding to the second layer for forming a contacting bilayer
24 arrangement therewith. The push layer comprising the osmopolymer, or
25 osmopolymer and osmagent, is placed in contact with the first drug layer.
26 The push layer, a displacement layer for displacing the drug layer from the
27 dosage form, is manufactured using the techniques for providing the first drug
28 layer. The layering of the first drug layer and the second displacement layer
29 can be fabricated by conventional press layering techniques. The bilayered
30 compartment-forming core is surrounded and coated with an outer wall
31 comprising a semipermeable composition. An exit is laser drilled through the

1 wall to contact the first drug layer. The dosage form is optically oriented
2 automatically by the laser equipment for forming the exit passageway.

3 In another manufacture, the dosage form is manufactured by the wet
4 granulation technique. In the wet granulation technique, for example, the
5 drug and the ingredients comprising a drug layer are blended using an
6 organic solvent, such as isopropyl alcohol-methylene dichloride 80:20 v:v
7 (volume:volume), or methanol-methylene dichloride, as the granulation fluid.
8 Other granulating fluid, such as denatured alcohol 100%, can be used for this
9 purpose. The ingredients forming the drug layer are individually passed
10 through a screen and then thoroughly blended in a mixer. Next, other
11 ingredients comprising the drug layer are dissolved in a portion of the
12 granulation fluid, such as the solvents described above. Then, the latter
13 prepared wet blend is slowly added to the drug blend with continual mixing in
14 the blender. The granulating fluid is added until a wet blend is produced,
15 which wet mass is forced through a screen onto oven trays. The blend is
16 dried for 7 to 24 hours at 30°C to 50°C. The dry granules are then sized with
17 a screen. Next, a lubricant is passed through a screen and added to the dry
18 screen granule blend. The granulation is put into milling jars and mixed on a
19 jar mill for 1 to 15 minutes. The other drug layer and the displacement layers
20 are made by the same wet granulation techniques. The compositions are
21 pressed into their individual layers in standard presses, such as a layer press.

22 Another manufacturing process that can be used for providing the
23 compartment-forming compositional layers comprises blending the powdered
24 ingredients for each layer independently in a fluid bed granulator. After the
25 powdered ingredients are dry blended in the granulator, a granulating fluid,
26 for example, poly(vinylpyrrolidone) in water, or in denatured alcohol, or in
27 95:5 ethyl alcohol/water, or blends of ethanol and water, is sprayed onto the
28 powders. Optionally, the ingredients can be dissolved or suspended in the
29 granulating fluid. The coated powders are then dried in a granulator. This
30 process granulates all the ingredients present therein while adding the
31 granulating fluid. After the granules are dried, a lubricant, such as stearic

1 acid, calcium stearate, magnesium oleate, potassium oleate, or magnesium
2 stearate, is added to the granulator. The granules for each separate layer
3 are then pressed in the manner described above.

4 The dosage form of this invention is manufactured in another
5 manufacture by first mixing a known dose of drug with compositional layer-
6 forming ingredients, and then pressing under one-eighth to three tons the
7 composition into a solid layer possessing dimensions that correspond to the
8 internal dimensions of the compartment of the dosage form. The contacting
9 second layer, comprising an osmopolymer, or an osmopolymer and an
10 osmagent, is manufactured in a like manner. In another manufacture, the first
11 and second layers independently are manufactured by mixing the drug and
12 composition forming ingredients and a solvent into a solid, or into a semisolid,
13 by conventional methods such as ball milling, calendering, stirring or roller
14 milling, and pressed into a layer. Next, the first layer is placed next to a layer
15 of a displacement composition comprising an osmopolymer and an optional
16 osmagent. Then, the two-layered core is surrounded with a semipermeable
17 wall. The layering of the first layer and the second layer can be accomplished
18 by layer tablet press technique and longitudinal compressed tablet technique.

19 A wall can be applied by molding, spraying or dipping the pressed-shape
20 bilayered core into wall forming materials. Another technique that can be
21 used for applying the wall is the air-suspension coating procedure. This
22 procedure consists in suspending and tumbling the two-layered laminate
23 in a current of air until the wall forming composition surrounds the bilayer.
24 The air-suspension procedure is described in U.S. Patent No. 2,799,241;
25 J. Am. Pharm. Assoc., Vol. 48, pp. 451-459 (1979); and ibid., Vol. 49,
26 pp. 83-84 (1960). Other manufacturing procedures are described in
27 Modern Plastic Encyclopedia, Vol. 46, pp. 62-70 (1969); and in
28 Pharmaceutical Sciences, Remington, 14th Ed., pp. 1626-1979 (1970),
29 published by Mack Publishing Co., Easton, PA.

30 Exemplary solvents suitable for manufacturing the wall, the layer and
31 the wall include inert inorganic and organic solvents. The solvents broadly

1 include members selected from the group consisting of aqueous solvents,
2 alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated
3 solvents, cycloaliphatics, aromatics, heterocyclic solvents and mixtures
4 thereof. Typical solvents include acetone, diacetone alcohol, methanol,
5 ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate,
6 isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl
7 ketone, n-hexane, n-heptane ethylene glycol monoethyl ether, ethylene
8 glycol monoethyl acetate, methylene dichloride, ethylene dichloride,
9 propylene dichloride, carbon tetrachloride, chloroform, nitroethane,
10 nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane,
11 cyclooctane, benzene, toluene, naphtha, tetrahydrofuran, diglyme, aqueous
12 and nonaqueous mixtures thereof, such as acetone and water, acetone and
13 methanol, acetone and ethyl alcohol, methylene dichloride and methanol,
14 ethylene dichloride and methanol, and methylene dichloride and ethanol.
15 The solvents are disclosed in U.S. Patent No. 5,030,456.

16

17 DETAILED DESCRIPTION OF THE EXAMPLES

18

19 The following examples are illustrative of the present invention, and the
20 examples should not be considered as limiting the scope of the invention in
21 any way, as these examples, and other equivalents thereof, will become
22 apparent to those versed in the art in the light of the present disclosure and
23 the accompanying claims.

24

25 EXAMPLE 1

26

27 An osmotic dosage form designed and shaped to deliver a drug that
28 stimulates the central nervous system by administering a drug in an
29 ascending release profile is manufactured as follows: First, a binder solution
30 is prepared as follows: 300 g of poly(vinylpyrrolidone) having a number-
31 average molecular weight of 40,000 is added to a mixing vessel containing

1 2700 g of distilled water. The mixture is stirred until the poly(vinylpyrrolidone)
2 dissolves in the water and produces a clear solution. Next, a drug formulation
3 is prepared as follows: 6,564 g of poly(ethylene oxide) having a number-
4 average molecular weight of 200,000 is passed through a 40 mesh screen.
5 Then, 3,282 g of the screened poly(ethylene oxide) is placed into the bowl of
6 a fluid bed granulator. Next, 1,024 g of central nervous system acting
7 methylphenidate hydrochloride is placed into the granulator with the
8 poly(ethylene oxide). Then, 100 g poly(vinylpyrrolidone) of number-average
9 molecular weight 40,000 is added to the granulator; then the remaining
10 3,182 g of poly(ethylene oxide) is added to the granulator. The addition of
11 the dry ingredients into the bowl is performed so that the methylphenidate
12 hydrochloride is located between two layers of poly(ethylene oxide). The
13 granulation is started with the ingredients inside the bowl fluidized for
14 2 minutes to obtain a uniform mixing of the powders. Next, the binder
15 solution is sprayed onto the powder bed through nozzles at a spray rate of
16 100 g/min. During the spraying process, the airflow is maintained at 500 cfm
17 and the temperature kept at 25°C. During the spraying operation, the solution
18 is sprayed for 30 seconds, followed by a shaking time of 10 seconds during
19 which time the powders adhering to the filterbags are dislodged into the
20 granulating chamber. At the end of the spraying operation, the granules are
21 dried in the granulating chamber for an additional 5 to 10 minutes to obtain
22 dry granulation. The methylphenidate hydrochloride granules are passed
23 through a fluid air mill with a 7 mesh screen for size reduction. The screen
24 is U.S. Sieve Series as disclosed in Chemical Engineer's Handbook, Perry,
25 6th Ed., pp. 21-15 (1984). Next, the screened granules are placed in a
26 blender to which 8 g of magnesium stearate (screened through a 40 mesh
27 screen) and 4 g of powdered butylated hydroxy toluene (screened through a
28 60 mesh screen) is added to the granules and mixed together.

29 Next, the displacement or push composition is prepared as follows:
30 First a binder solution is prepared by adding 937.5 g of poly(vinylpyrrolidone)
31 of 40,000 number-average molecular weight to 8437.5 g of distilled water.

1 This mixture is stirred until the poly(vinylpyrrolidone) dissolves in water to
2 yield a clear solution. Next, displacement osmotic granules are prepared as
3 follows: First, 13452.5 g of poly(ethylene oxide) having a number-average
4 molecular weight of 7,000,000 is placed into the bowl of a fluid bed
5 granulator. Next, 312.5 g of poly(vinylpyrrolidone) of 40,000 number-average
6 molecular weight is added to the bowl. Then, 10,000 g of osmagent sodium
7 chloride and 250 g of red ferric oxide, which have been milled using a
8 21 mesh screen, are placed into the bowl. The bowl is attached to the main
9 body of the granulator and the granulation is initiated. Initially, the powder
10 bed inside the bowl is fluidized for 3 minutes to obtain uniform mixing of the
11 powders. Then, the binder solution is sprayed onto the powder bed and the
12 binder solution sprayed thereon at a rate of 240 g/min. During the spraying,
13 the air flow is maintained at 1000 cfm and the temperature kept at 25°C.
14 The solution is sprayed for 30 seconds, followed by shaking for 10 seconds,
15 during which time the powders adhering to the filterbags can be dislodged
16 into the granulating chamber. At the end of the spraying operation, the
17 granules are dried in the granulating chamber for an additional 10 to 15
18 minutes to obtain dry granulation. The granules are then passed through
19 an air mill with a 7 mesh screen for size reduction. The granules are then
20 transferred to a blender, and 25 g of magnesium stearate (screened through
21 a 40 mesh screen) and 12.5 g of butylated hydroxy toluene (screened
22 through a 60 mesh screen) are added to the granules and mixed together.
23 Next, the drug composition comprising the methylphenidate and the
24 displacement osmotic composition are compressed together using an
25 automated tablet compression machine capable of compressing the two
26 layers longitudinally together. First, 110 mg of the methylphenidate
27 composition forming layer is added to the die cavity of 4.7 mm diameter,
28 tamped, and then 132 mg of the displacement osmotic composition is placed
29 into the die and compressed together using 0.2 metric tons of pressure.

1 Next, a wall-forming composition comprising 90% cellulose acetate
2 having an acetyl content of 39.8%, and 10% poly(ethylene glycol) having
3 an average molecular weight of 3350 is formed around the bilayered core.
4 The semipermeable composition is dissolved in a mixture of acetone and
5 water (90:10 wt:wt) to provide solid composition of the solution at 5%.
6 The compressed bilayered cores are placed into a 61 cm coating pan and
7 the coating solution sprayed onto the cores at a spray rate of 100 ml/min.
8 The temperature is kept at 35°C during the coating process.

9 Next, one 30 mil (0.76 mm) orifice is drilled through the semipermeable
10 wall connecting the drug composition with the exterior of the dosage form.
11 The residual solvent is removed by drying at 45°C and 45% relative humidity
12 in an oven for 48 hours. At the end of the drying cycle, the humidity is turned
13 off, and the dosage forms are dried at 45°C for an additional 4 hours.

14 The dosage form prepared according to this example comprises a first
15 drug layer comprising 110 mg consisting of 14.08 mg of methylphenidate,
16 90.26 mg of poly(ethylene oxide) of 200,000 number-average molecular
17 weight, 5.5 mg of poly(vinylpyrrolidone) of 40,000 number-average molecular
18 weight, 0.11 mg of magnesium stearate, and 0.055 mg of butylated hydroxy
19 toluene. The dosage form displacement layer 2 comprises 132 mg
20 composed of 71.032 mg of poly(ethylene oxide) of 7,000,000 number-
21 average molecular weight, 52.8 mg of osmagent sodium chloride, 6.6 mg of
22 poly(vinylpyrrolidone) of 40,000 number-average molecular weight, 1.32 mg
23 of red ferric oxide, 0.132 mg of magnesium stearate, and 0.066 mg of
24 butylated hydroxy toluene. The semipermeable wall weighed 17 mg and
25 comprised 15.3 mg of cellulose acetate consisting of 39.8% acetyl content,
26 and 1.7 mg of poly(ethylene glycol) of 3350 number-average molecular
27 weight. The dosage form possessed a 30 mil (0.76 mm) orifice.

28 The dosage form delivered methylphenidate in an ascending release
29 rate. The dosage from delivered 0.22 mg in the first hour, 1.45 mg in the
30 second hour, 1.72 mg in the third hour, 1.84 mg in the fourth hour, 2.05 mg in
31 the fifth hour, 2.21 mg in the sixth hour, 2.13 mg in the seventh hour, 1.26 mg

1 in the eighth hour, 0.39 mg in the ninth hour, and 0.09 mg in the tenth hour,
2 with a residual of 0.72 mg in the dosage form.

3

4

EXAMPLE 2

5

6 The procedure of Example 1 is followed with the processing steps as
7 previously described, except the drug in this example is a member selected
8 from the group consisting of pemoline, deanol, deanol acetamidobenzoate,
9 benzphetamine hydrochloride, deanol aceglumate, clortermine,
10 diethylpropion, fenfluramine, dextroamphetamine phosphate, and
11 dextroamphetamine sulfate.

12

13

EXAMPLE 3

14

15 An osmotic dosage form adapted, designed and shaped as an
16 oral tablet for delivering a drug with an ascending release profile is
17 manufactured as follows: First, a composition is prepared by passing
18 through a 40 mesh screen 393.85 g of poly(ethylene oxide) having a
19 molecular weight of about 300,000. Then 63.65 g of drug selected from
20 the group consisting of amphetamine sulfate, difluanine hydrochloride,
21 flubanilate, mefexamide, methamphetamine, pseudoephedrine and
22 pyrovalerone hydrochloride; 15.00 g of polyoxyl 40 stearate; and 25.00 g
23 of hydroxypropylmethylcellulose having a number-average molecular weight
24 of 11,200 are screened to 40 mesh and then added to the poly(ethylene
25 oxide). The four ingredients are mixed for about 10 minutes in a conventional
26 mixer. Then 50 ml of denatured, anhydrous ethanol is slowly added to the
27 mixer and the mixing continued for an additional 10 minutes. The wet
28 granulation is passed through a 20 mesh screen, dried at room temperature
29 for 16 hours, and passed again through a 20 mesh screen. Finally, 2.5 g of
30 magnesium stearate is added to the granulation and all the ingredients mixed
31 for an additional 3 minutes.

1 Next, a second displacement composition is prepared by mixing
2 267.5 g of poly(ethylene oxide) having a number-average molecular weight of
3 7,000,000 with 175 g (35%) of osmagent sodium chloride; 25 g of Carbomer®
4 934, a carboxyvinyl polymer possessing a 3,000,000 number-average
5 molecular weight, disclosed in U.S. Patent Nos. 3,074,852, 3,634,584, and
6 4,248,847, commercially available from BF Goodrich Chemicals, Cleveland,
7 OH; and 5 g of red iron oxide. The homogenous blend is passed through a
8 40 mesh screen, and 25 g of hydroxypropylmethylcellulose having a number-
9 average molecular weight of 11,200 is added to all the ingredients. The
10 ingredients are blended in a conventional planetary mixer for 10 minutes.
11 Then, 50 ml of denatured, anhydrous ethanol is slowly added to the blending
12 mixture and all the ingredients mixed for an additional 5 minutes. The freshly
13 prepared wet granulation is passed through a 20 mesh screen, allowed to dry
14 at room temperature for 16 hours, and again passed through a 20 mesh
15 screen. The screened granulation is mixed with 2.5 g of magnesium stearate
16 for 3 minutes.

17 A laminating press is used to form the bilaminate. First, 110 mg of
18 the first drug composition is added to a 4.7 mm die cavity and tamped. Then,
19 115 mg of the second expandable composition is added to the die cavity, and
20 the two separate compositions pressed into a bilaminated core under 1/2 ton
21 of pressure.

22 Next, the bilaminated core is surrounded with a semipermeable wall.
23 The wall-forming composition comprises 95% cellulose acetate having an
24 acetyl content of 39.8%, and 5% polyethylene glycol having a molecular
25 weight of 3350. The wall forming composition is dissolved in acetone:water
26 (90:10 wt:wt) solvent to make a 5% solids solution. Then, 22 mg of the wall
27 forming composition is sprayed onto and around this bilaminate in a Hi-Coater
28 pan coater. Then, a 30 mil (0.76 mm) exit orifice is drilled by laser or
29 mechanical drill in the center of the drug laminate side of the osmotic device.
30 The residual solvent is removed by drying for 48 hours at 50°C and 50%
31 relative humidity, followed by one hour drying at 50°C.

1 A dosage form prepared by this example comprises a 110 mg drug
2 layer comprising 12.73 wt% pseudoephedrine hydrochloride, 78.77 wt%
3 poly(ethylene oxide) of 300,000 number-average molecular weight, 5 wt%
4 hydroxypropylmethylcellulose of 11,200 number-average molecular weight,
5 3 wt% polyoxyl 40 stearate and 0.5 wt% magnesium stearate. The 115 mg
6 displacement layer comprises 53.5 wt% poly(ethylene oxide) possessing a
7 7,000,000 number-average molecular weight, 5 wt%
8 hydroxypropylmethylcellulose possessing 11,200 number-average
9 molecular weight, 35 wt% sodium chloride, 0.5 wt% magnesium stearate,
10 5 wt% Carbopol® carboxyvinylpolymer, and 1 wt% red ferric oxide. The
11 semipermeable wall comprises 20.9 mg of cellulose acetate of 39.8% acetyl
12 content and 1.1 mg of poly(ethylene glycol) of 4,000 number-average
13 molecular weight. The dosage form comprises a 30 mil orifice (0.76 mm)
14 and exhibits the ascending release rate profile seen in accompanying
15 Figure 1.

17 EXAMPLE 4

19 A dosage form designed and adapted as a tablet for the oral
20 administration of methylphenidate pharmaceutically acceptable salt in an
21 ascending release profile is manufactured as follows: First, 163.4 g of
22 poly(ethylene oxide) having an average molecular weight of 200,000 is
23 passed through a 40 mesh screen and placed into the bowl of a conventional
24 planetary mixer. Next, 25.6 g of methylphenidate hydrochloride is weighed
25 and placed into the bowl containing the poly(ethylene oxide). Next, 10 g of
26 hydroxypropylmethylcellulose possessing a 11,200 molecular weight is
27 passed through a 40 mesh screen and placed into the bowl containing the
28 poly(ethylene oxide) and methylphenidate hydrochloride. Next, 0.5 g of
29 FD&C Blue Dye No. 1 is placed into the bowl of the mixer. The four
30 ingredients are blended together in the planetary mixer for 10 minutes.
31 Next, 100 ml of denatured anhydrous ethanol is gradually added to the

1 mixer with continued mixing for 10 minutes to change the consistency of the
2 dry powder to that of granules. The wet granulation is then passed through
3 a 20 mesh screen, dried at room temperature for 16 hours, and then passed
4 through a 20 mesh screen. Next, 0.5 g of magnesium stearate, which has
5 been passed through a 40 mesh screen, is added to the granulation, and all
6 the ingredients are mixed for an additional 1 minute.

7 Next, a displacement layer is manufactured as follows: First, 107 g of
8 poly(ethylene oxide) having an average molecular weight of 7,000,000, 80 g
9 of sodium chloride (40%), 10 g of hydroxypropylmethylcellulose (USP grade)
10 possessing a 11,200 molecular weight, and 2 g of red ferric oxide are passed
11 through a 40 mesh screen and then placed into the bowl of a conventional
12 planetary mixer. The powder mixture is then blended together until a
13 homogenous blend is formed. Next, 50 ml of denatured anhydrous ethanol is
14 added to the mixer with continued mixing over a period of 5 to 10 minutes,
15 such that the consistency of the dry powder changes to granules. The wet
16 granulation is passed through a 20 mesh screen, dried at room temperature
17 for 16 hours, and then passed through a 20 mesh screen. Next, 1 g of
18 magnesium stearate which has been passed through a 40 mesh screen is
19 added to the granulation, and all the ingredients are mixed for an additional
20 1 minute.

21 Next, a bilayer press is used to compress the two layers together to
22 form a tablet dosage form. First, 110 mg of the drug composition is added to
23 the 4.7 mm die cavity and lightly tamped. Next, 115 mg of the displacement
24 composition is weighed and placed into the die cavity, and the two layers are
25 compressed together using 1/2 ton of pressure to form a bilayer pretablet.

26 A wall for enveloping the bilayer pretablet to yield the finished tablet is
27 formed as follows: First, a semipermeable composition composed of 90%
28 cellulose acetate (having an acetyl content of 39.8%) and 10% polyethylene
29 glycol having an average molecular weight of 3350 is prepared by dissolving
30 in a mixture of acetone and water (the solvents are mixed together in a ratio
31 of 90:10 wt:wt), such that the solids composition of the solution is 5%. The

1 bilayer tablets are placed in a coater pan, and 20 mg of the semipermeable
2 composition is sprayed on to the bilayer tablets. Next, a 30 mil (0.76 mm)
3 orifice is drilled on the drug layer side of the bilayer tablet using an automatic
4 tableting positioning laser drill. Next, the semipermeable coated tablets are
5 dried for 48 hours at 50°C and 50% relative humidity to remove the residual
6 solvents. The release rate ascending profile for a dosage form prepared
7 according to the example is seen in accompanying Figure 2. Drawing
8 Figure 2 depicts the release of methylphenidate hydrochloride from a
9 semipermeable, longitudinal dosage form.

11 EXAMPLE 5

12
13 The procedure of the above examples is followed, with the further
14 embodiment that a drug overcoat and an optional taste-masking coat is
15 overcoated onto the exterior surface of the wall. The overcoat, in one
16 manufacture, comprises 60 wt% of hydroxypropylmethylcellulose of
17 9,200 number-average molecular weight and 40 wt% methylphenidate
18 hydrochloride. The hydroxypropylmethylcellulose is added to water
19 and mixed until a uniform solution results. Then, the methylphenidate
20 hydrochloride is added to the solution and mixed such that a clear
21 solution results. The final solution has a solid composition of 10%.
22 Next, semipermeable walled dosage forms are placed in a coater and 10 mg
23 of the drug overcoat is sprayed onto the semipermeable wall that surrounds
24 the internal bilayer compressed tablet. Then, overcoated dosage forms are
25 dried for 10 minutes at 40°C. For taste masking, a suspension of Opadry®,
26 a powder blend comprised of hydroxypropylmethylcellulose, titanium dioxide,
27 polyethylene glycol and polysorbate 80, is prepared in water to effect a solid
28 content of 10%. The drug overcoated dosage forms are placed in a coater
29 and 9 mg of the taste-masking solution is sprayed over the drug overcoat to
30 produce a double-overcoated dosage form. Next, the dosage forms are dried
31 at 40°C for 10 to 12 minutes to yield the operable dosage forms.

EXAMPLE 6

The procedures set forth in the above examples are followed, with the manufactures as described above, except in this invention, a first dosage form is provided wherein the drug layer comprises 28 mg of methylphenidate hydrochloride, and a second dosage form is provided wherein the drug layer comprises 42 mg of methylphenidate hydrochloride.

EXAMPLE 7

The procedures set forth in the above examples are followed with the manufacturing conditions set forth as previously indicated, except that in this example a dosage form is provided wherein the second displacement layer comprises 65 mg of sodium carboxymethylcellulose osmopolymer of 3,500,000 number-average molecular weight and an osmagent combination comprising 58 mg of dextrose-fructose in equal proportions; and a dosage form wherein the second displacement layer comprises 72 mg of poly(ethylene oxide)-poly(propylene oxide) copolymer of 7,900,000 number-average molecular weight and 47.8 mg of co-osmagent sodium chloride-dextrose (23.9 mg - 23.9 mg).

EXAMPLE 8

A dosage form designed and adapted to deliver a drug in an ascending release rate profile is manufactured according to this example.

First, a first layer-forming composition comprising a dose of drug is manufactured as follows: 157.8 mg of poly(ethylene oxide) having a number-average molecular weight of 200,000 is passed through a 40 mesh screen (U.S. Sieve) and placed into the bowl of a conventional planetary mixer.

Next, 31.2 g of the drug methylamphetamine hydrochloride is added to the

1 mixer. Then, 10 g of hydroxypropylmethylcellulose of 16,000 number-
2 average molecular weight is passed through a 40 mesh screen and added
3 to the mixer comprising the methylamphetamine hydrochloride and the
4 poly(ethylene oxide). Then, 0.5 g of FD&C Blue Dye No. 1, for color
5 identification, is added to the bowl of the mixer. The ingredients are blended
6 in the mixer for 10 minutes to produce a homogenous composition. Next,
7 100 ml of denatured anhydrous ethanol is added gradually to the mixer, with
8 continual mixing over a period of 5 to 10 minutes to change the consistency of
9 the dry ingredients to wet granules. The wet granulation is passed through a
10 20 mesh screen, dried at room temperature for 16 hours, and then passed
11 through a 20 mesh screen. Then, 0.5 g of magnesium palmitate is passed
12 through a 40 mesh screen, added to the homogenous composition, and all
13 the ingredients mixed for an additional minute.

14 Next, a displacement layer, the second layer, is prepared as follows:
15 First, 53 g of poly(ethylene oxide) of 7,500,000 number-average molecular
16 weight, 54 g of poly(propylene oxide) of 5,000,000 number-average
17 molecular weight, 80 g of osmagent sodium chloride, 10 g of
18 hydroxypropylethylcellulose of 24,000 number-average molecular
19 weight, and 2 g of red ferric oxide are passed through a 40 mesh screen
20 and then placed into the bowl of a mixer. The ingredients are blended
21 together to form a homogenous blend. Next, 50 ml of denatured anhydrous
22 ethanol is added to the mixer, accompanied by continual mixing for
23 10 minutes to produce wet granules. The wet granules are passed through
24 a 20 mesh screen, dried at room temperature for 16 hours, and then passed
25 through a 20 mesh screen. Next, 1 g of stearic acid lubricant is passed
26 through a 40 mesh screen, added to the granulation, and all the ingredients
27 mixed for an additional minute.

28 Next, the first drug layer-forming composition and the second
29 displacement layer-forming composition are pressed together into contacting
30 layers as follows: First, 33 mg of the first composition is added to a 0.55 cm
31 die cavity and tamped lightly. Then, 57 mg of the displacement composition

1 is added to the die and tamped lightly, to provide two layers that are
2 compressed using 1/2 ton of pressure to form a bilayer tablet.

3 Next, the bilayer is surrounded with a semipermeable wall as follows:

4 First, a semipermeable wall forming composition is prepared comprising
5 95% cellulose having an acetyl content of 39.8%, and 5% polyethylene glycol
6 of 3350 number-average molecular weight (available from Union Carbide Co.)
7 by dissolving the ingredients in a mixture of acetone and water in a 90:10
8 (v:v) ratio to provide solid composition at 5%. The bilayer tablets are placed
9 in a pan coater and 15 mg of the semipermeable wall forming composition is
10 sprayed onto the bilayer tablet. Next, a 30 mil (0.76 mm) orifice is drilled on
11 the drug side to connect the first layer with the outside of the dosage form.
12 The dosage form tablets are dried at 50°C and 50% relative humidity to
13 remove the residual solvents. The dosage form comprises 5.2 mg of
14 methamphetamine hydrochloride to give an extended ascending release
15 tablet. Additional dosage forms are provided according to the invention
16 comprising 10 mg and 15 mg methamphetamine hydrochloride extended
17 ascending release tablet.

18

19 EXAMPLE 9

20

21 The above examples are followed to provide a dosage form comprising
22 an external coat of a pharmaceutically acceptable drug and an internal
23 composition comprising a pharmaceutically acceptable drug, which dosage
24 form when in operation in a fluid biological environment delivers the external
25 overcoat drug in 0 to 1 hour, and delivers the internal drug in the amounts of
26 15% in 0 to 2 hours, 30% in 2 to 4 hours, 33% in 4 to 6 hours, 18% in 6 to
27 8 hours, and 4% in 8 to 10 hours.

EXAMPLE 10

The above examples are followed to provide a dosage form comprising an external overcoat comprising 100 ng to 100 mg of drug and an internal composition comprising 10 ng to 500 mg of drug, which dosage form when in operation in the fluid environment of the gastrointestinal tract delivers the 100 ng to 100 mg external overcoat in 0 to 1 hour, and delivers the internal 10 ng to 500 mg in an increasing release of 20% in 0 to 4 hours, 30% in 4 to 8 hours, 40% in 8 to 12 hours and 10% in 12 to 16 hours, to substantially overcome tolerance to delivered drug.

EXAMPLE 11

An osmotic dosage form designed and shaped to deliver methylphenidate hydrochloride to a patient in need of methylphenidate therapy in an ascending release profile is manufactured as follows:

Composition of drug layer 1: The following procedure is used to manufacture 8,000 g of layer 1 composition:

A. Preparation of binder solution.

260 g of hydroxypropylmethylcellulose having average molecular weight of 11,200 is added to a mixing vessel containing 3250 g of water. This mixture is stirred until the hydroxypropylmethylcellulose dissolves in water and a clear solution is formed. This solution is referred to as the binder solution.

B. Preparation of methylphenidate hydrochloride granules.

4380 g of polyethylene oxide having an average molecular weight of 200,000 is passed through a 40 mesh screen. Then, 2190 g of the screened poly(ethylene oxide) is placed into the bowl of a fluid bed granulator. Next, 2032 g of sorbitol is added to the powder bed, followed by 1024 g of methylphenidate hydrochloride into the bowl over the poly(ethylene oxide). Next, 140 g of hydroxypropylmethylcellulose is added

1 to the bowl. The remaining 2190 g of poly(ethylene oxide) is then added to
2 the bowl. The addition of dry ingredients into the bowl is performed so that
3 the methylphenidate hydrochloride is located in between the two layers of
4 poly(ethylene oxide). The bowl is attached to the main body of the granulator
5 and the granulation process is initiated. Initially, the powder bed inside the
6 bowl is fluidized for 2 minutes to obtain uniform mixing of the powders. Next,
7 the binder solution is sprayed onto the powder bed through nozzles such that
8 the solution is sprayed at a rate of 60 g/min. During the spraying process,
9 the process air flow is maintained at 500 cfm and the product temperature is
10 maintained at 22°C. During the spraying operation, the solution is sprayed for
11 30 seconds followed by a shaking time of 10 seconds, during which time the
12 powders adhering to the filterbags may be dislodged into the granulating
13 chamber. At the end of the spraying operation, the granules are dried in the
14 granulating chamber for an additional 5 to 10 minutes to obtain dry
15 granulation. The methylphenidate hydrochloride granules are then passed
16 through a fluid air mill with a 7 mesh screen for size reduction. The size-
17 reduced granules are then placed into a suitable blender. 160 g of
18 magnesium stearate (screened through a 40 mesh screen) and 4 g of
19 powdered butylated hydroxy toluene (screened through a 60 mesh screen)
20 are added to the granules and mixed together.

21 Composition of layer 2: The following procedure is used to manufacture
22 8,000 g of displacement layer 2 composition:

23 A. Preparation of binder solution.

24 260 g of hydroxypropylmethylcellulose having an average molecular
25 weight of 11,200 is added to a mixing vessel containing 3250 g of water.
26 This mixture is stirred until the hydroxypropylmethylcellulose dissolves in
27 water and a clear solution is formed. This solution is referred to as the binder
28 solution.

29 B. Preparation of osmotic layer granules.

30 4308 g of poly(ethylene oxide) having an average molecular weight of
31 7,000,000 is placed into the bowl of a fluid bed granulator. Next, 140 g of

1 hydroxypropylmethylcellulose having an average molecular weight of 11,200
2 is added to the bowl. Then, 3,200 g of sodium chloride and 80 g of red ferric
3 oxide, which have been screened using a 21 mesh screen, are then placed
4 into the bowl. The bowl is attached to the main body of the granulator and
5 the granulation process is then initiated. Initially, the powder bed inside the
6 bowl is fluidized for 3 minutes to obtain uniform mixing of the powders. Next,
7 the binder solution is sprayed onto the powder bed through nozzles, such that
8 the solution is sprayed at a rate of 80 g/min. During the spraying process, the
9 process air flow is maintained at 400 cfm, and the product temperature is
10 maintained at 22°C. During the spraying operation, the solution is sprayed for
11 30 seconds followed by a shaking time of 10 seconds, during which time the
12 powders adhering to the filterbags may be dislodged into the granulating
13 chamber. At the end of the spraying operation, the granules are dried in the
14 granulating chamber for an additional 10 to 15 minutes to obtain dry
15 granulation. The process parameters may be adjusted to obtain a quality
16 product. The granules then are passed through a fluid air mill with a 7 mesh
17 screen for size reduction. The size-reduced granules are then placed into a
18 suitable blender. Next, 8 g of magnesium stearate (screened through a
19 40-mesh screen) and 4 g of powdered butylated hydroxy toluene (screened
20 through a 60 mesh screen) are added to the granules and mixed together.

21 C. Compression of the layers.

22 The methylphenidate granules-forming layer and the osmotic granules-
23 forming layer are compressed together using an automated tablet
24 compression machine capable of compressing the two layers together
25 longitudinally. First, 110 mg of methylphenidate granules (layer 1) is added
26 into the die cavity of a 3/16" diameter modified ball tooling, tamped, and then
27 132 mg of the osmotic layer granulation (layer 2) is placed into the die and
28 compressed together using 0.2 metric tons of pressure.

29 D. Application of semipermeable membrane wall.

30 The semipermeable membrane wall is composed of 47.5% cellulose
31 acetate (having an acetyl content of 39.8), 47.5% cellulose acetate (having an

1 acetyl content of 32.0), and 5% polyethylene glycol having an average
2 molecular weight of 3350. The semipermeable membrane-forming
3 composition is dissolved in a mixture of methylene chloride and methanol
4 (the solvents are mixed together in a ratio of 80:20 wt:wt); such that the solids
5 composition of the solution is 4%. The compressed systems are placed into a
6 61 cm coating pan and the coating solution is sprayed onto the tablets such
7 that the solution is sprayed at a rate of 100 ml/min/gun. The product
8 temperature is maintained at 25°C; the coating process is stopped when the
9 semipermeable membrane composition has been sprayed onto the
10 compressed systems.

11 Next, one 30 mil (0.76) orifice is drilled, using a mechanical drill bit or a
12 laser, on the drug layer side of the coated systems. The residual solvents
13 remaining after the coating are removed by drying the systems at 45°C and
14 45% relative humidity in an oven for 48 hours. At the end of this drying cycle,
15 the humidity is turned off, and the systems are dried at 45°C for an additional
16 4 hours to complete the drying process.

17 A methylphenidate dosage form assembled as described contains
18 110 mg of drug containing layer 1, which is composed of 12.8%
19 methylphenidate hydrochloride, 54.75% poly(ethylene oxide) of average
20 molecular weight 200,000, 25.4% sorbitol, 5% hydroxypropylmethylcellulose
21 of average molecular weight 11,200, 2% magnesium stearate and 0.05%
22 butylated hydroxy toluene. The dosage form also contains 132 mg of layer 2,
23 composed of 53.85% poly(ethylene oxide) of average molecular weight
24 7,000,000, 40% sodium chloride, 5% hydroxypropylmethylcellulose of
25 average molecular weight 11,200, 1% red ferric oxide, 0.1% magnesium
26 stearate and 0.05% butylated hydroxy toluene. The 42 mg semipermeable
27 laminate is composed of 47.5% cellulose acetate of acetyl content 39.8% and
28 47.5% cellulose acetate of acetyl content 32.0%, and 5% polyethylene glycol
29 having an average molecular weight of 3350 is applied to the compressed
30 bilayer system. A 30 mil (0.76 mm) orifice is drilled on the drug layer side
31 as the exit orifice. The final system is capable of delivering 14 mg of

1 methylphenidate hydrochloride with an ascending release rate profile
2 over time.

3 The dosage form delivered methylphenidate hydrochloride in an
4 ascending rate. The dosage form delivered 0.13 mg in the first hour, 1.16 mg
5 in the second hour, 1.53 mg in the third hour, 1.61 mg in the fourth hour,
6 1.75 mg in the fifth hour, 1.79 mg in the sixth hour, 2.13 mg in the seventh
7 hour, 2.18 mg in the eighth hour, 1.07 mg in the ninth hour, and 0.43 mg in
8 the tenth hour, 0.17 mg in the eleventh hour, and 0.13 mg in the twelfth hour.

9

10 EXAMPLE 12

11

12 An osmotic dosage form designed, shaped and adapted for delivering
13 methylphenidate pharmaceutically acceptable salt to a patient in need of
14 methylphenidate therapy in an ascending release rate profile is manufactured
15 as follows: First, the procedure used to manufacture the drug layer
16 granulation in Example 11 is followed in this example. The composition of
17 the drug layer can comprise from 0% to 30% sorbitol. Next, the following
18 procedure is used to manufacture the displacement layer:

19 A. Preparation of binder solution.

20 400 g of hydroxypropylmethylcellulose having an average molecular
21 weight of 11,200 is added to a mixing vessel containing 5000 g of water.
22 This mixture is stirred until the hydroxypropylmethylcellulose dissolves in
23 water and a clear solution is formed. This solution is referred to as the binder
24 solution.

25 B. Preparation of osmotic layer granules.

26 First, 3912 g of hydroxyethylcellulose having an average molecular
27 weight of 1,300,000 is placed into the bowl of a fluid bed granulator. Next,
28 400 g of hydroxypropylmethylcellulose having an average molecular weight of
29 11,200 is added to the bowl. Then, 3,200 g of sodium chloride and 80 g of
30 black ferric oxide, which have been milled using a 21 mesh screen, is then
31 placed into the bowl. The bowl is attached to the main body of the granulator

1 and the granulation process is then initiated. Initially, the powder bed inside
2 the bowl is fluidized for 3 minutes to obtain uniform mixing of the powders.
3 Next, the binder solution is sprayed at a rate of 80 g/min. During the spraying
4 process, the process air flow is maintained at 400 cfm and the product
5 temperature is maintained at 22°C. During the spraying operation, the
6 solution is sprayed for 30 seconds followed by a shaking time of 10 seconds,
7 during which time the powders adhering to the filterbags may be dislodged
8 into the granulating chamber. At the end of the spraying operation,
9 the granules are dried in the granulating chamber for a additional 10 to
10 15 minutes to obtain dry granulation. The process parameters may be
11 adjusted to obtain a quality product. The granules are then passed through
12 a fluid air mill with a 7 mesh screen for size reduction. The size-reduced
13 granules are then placed into a blender. Then, 8 g of magnesium stearate
14 (screened through a 40 mesh screen) and 4 g of powdered butylated hydroxy
15 toluene (screened through a 60 mesh screen) is added to the granules and
16 mixed together.

17 C. Compression of the layers.

18 The methylphenidate granules-forming layer and the osmotic granules-
19 forming layer are compressed together using an automated tablet
20 compression machine capable of compressing the two layers together
21 longitudinally. First, 110 mg of methylphenidate granules (layer 1) is added
22 into the die cavity of a 3/16" diameter tooling, tamped, and then 132 mg of the
23 osmotic layer granulation (layer 2) is placed into the die and compressed
24 together using 0.2 metric tons of pressure.

25 D. Application of semipermeable membrane wall.

26 The semipermeable membrane wall forming composition is composed
27 of 47.5% cellulose acetate 398 (having an acetyl content of 39.8), 47.5%
28 cellulose acetate 320 (having an acetyl content of 32.0) and 5% polyethylene
29 glycol having an average molecular weight of 3350. The semipermeable
30 membrane composition is dissolved in a mixture of methylene chloride and
31 methanol (the solvents are mixed together in a ratio of 80:20, wt:wt), such that

1 the solids composition of the solution is 4%. The compressed systems are
2 placed into a 24" coating pan and the coating solution is sprayed onto the
3 tablets such that the solution is sprayed at a rate of 100 ml/min/gun.
4 The product temperature is maintained at 35°C. The coating process is
5 stopped when the desired amount of semipermeable membrane composition
6 has been sprayed onto the compressed systems.

7 Next, one 30 mil (0.76 mm) orifice is drilled using a laser, on the drug
8 layer side of the coated systems. The residual solvents remaining after the
9 coating are removed by drying the systems at 45°C and 45% relative humidity
10 in an oven for 48 hours. At the end of this drying cycle, the humidity is turned
11 off and the systems are dried at 45°C for an additional 4 hours to complete
12 the drying process.

13 A methylphenidate dosage form assembled as described
14 contains 110 mg of drug containing layer 1, which is composed of 12.8%
15 methylphenidate hydrochloride, 50.2% to 80.2% poly(ethylene oxide)
16 of average molecular weight 200,000, 0 to 30% sorbitol,
17 5% hydroxypropylmethylcellulose of average molecular weight 11,200,
18 2% magnesium stearate, and 0.05% butylated hydroxy toluene.
19 The dosage form also contains 132 mg of layer 2, composed of 48.9%
20 hydroxyethylcellulose of average molecular weight 1,300,000, 40% sodium
21 chloride, 5% hydroxypropylmethylcellulose of average molecular weight
22 11,200, 1% red ferric oxide, 0.1% magnesium stearate and 0.05% butylated
23 hydroxy toluene. 42 mg of a semipermeable laminate composed of 47.5%
24 cellulose acetate of acetyl content 39.8%, 47.5% cellulose acetate of acetyl
25 content 32.0%, and 5% polyethylene glycol having an average molecular
26 weight of 3350 is applied to the compressed bilayer system, and a 30 mil
27 (0.76 mm) orifice is drilled on the drug layer side as the exit orifice. The final
28 system is capable of delivering 14 mg of methylphenidate hydrochloride with
29 an ascending release rate profile over a prolonged period of time.

EXAMPLE 13

The manufacturing procedures described in the above examples are followed, except that in this example a dosage form is provided wherein a drug overcoat and an optional taste-masking coat is overcoated onto the semipermeable walled dosage form. In this example, the drug layer is composed of 14 mg methylphenidate hydrochloride, 27.5 mg sorbitol, 5.5 mg polyvinylpyrrolidone, 61 mg of poly(ethylene oxide) of average molecular weight 2,000,000, 2.2 mg of magnesium stearate and 0.055 mg of butylated hydroxy toluene. The second displacement layer is composed of 72 mg of poly(ethylene oxide) of average molecular weight 7,000,000, 53 mg of sodium chloride, 6.6 mg of polyvinylpyrrolidone, 1.3 mg of ferric oxide, 0.132 mg of magnesium stearate, and 0.066 mg of butylated hydroxy toluene. The semipermeable wall is composed of 20 mg of cellulose acetate of average acetyl content 39.8%, 20 mg of cellulose acetate of average acetyl content 32% and 2 mg of poly(ethylene oxide) of average molecular weight 4000.

The drug-containing overcoat is composed of 60% hydroxypropylmethylcellulose and 40% methylphenidate hydrochloride. The hydroxypropylmethylcellulose is added to water and mixed until a uniform solution results. Then, the methylphenidate hydrochloride is added to this solution and mixed such that a clear solution results. The final solution has a solids composition of 10%. The semipermeable walled dosage forms are placed in a coater and 10 mg of the drug overcoat is sprayed onto the semipermeable wall that surrounds the internal bilayer compressed tablet.

Next, the tablets are dried in the coating pan at 40°C for 10-15 minutes. For the taste masking coat, a suspension of Opadry® is prepared in water such that the solids content is 10%. Opadry® is a powder blend commercially available from Colorcon Inc., and is composed of hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol and polysorbate 80. The systems coated with the drug containing overcoat are

1 placed into the coater, and the 9 mg of taste-masking coating solution is
2 sprayed onto the systems. Next, the systems are dried in the coating pan at
3 40°C for 10-15 minutes to yield the operable dosage forms.

4 The accompanying Figure 3 represents the functionality of the dosage
5 form of the example. The dosage form releases 4 mg of drug in the first
6 half hour from the drug overcoat, followed by 0.41 mg in the next half hour,
7 1.05 mg in the second hour, 1.49 mg in the third hour, 1.57 mg in the fourth
8 hour, 1.71 mg in the fifth hour, 1.75 mg in the sixth hour, 2.09 mg in the
9 seventh hour, 2.14 mg in the eighth hour, 1.32 mg in the ninth hour and
10 0.48 mg in the tenth hour.

11

12 EXAMPLE 14

13

14 The dosage form is manufactured as described in Example 13,
15 wherein in the second displacement layer the poly(ethylene oxide) is replaced
16 with 72 mg of hydroxyethylcellulose of 1,300,000 molecular weight.

17

18 EXAMPLE 15

19

20 Dosage forms are provided according to the above examples wherein:
21 (a) the dosage form comprises an overcoat of 8 mg of methylphenidate and
22 an internal composition comprising 28 mg of methylphenidate; and (b) the
23 dosage form comprises an overcoat of 12 mg of methylphenidate, and an
24 internal composition comprising 42 mg of methylphenidate.

25

26 EXAMPLES 16 TO 19

27

28 Dosage forms are provided by following the above disclosure and
29 examples to provide dosage forms that deliver a dose of drug, for example,
30 a central nervous system drug, in an ascending profile in the following
31 therapeutic ranges: (a) a dosage form that delivers in the first hour 0 to

1 0.308 mg of drug, in the second hour 0.250 mg to 2 mg of drug, in the third
2 hour 1 mg to 2.4 mg of drug, in the fourth hour 1.1 mg to 2.6 mg of drug, in
3 the fifth hour 1.23 mg to 2.9 mg of drug, in the sixth hour 1.33 mg to 3.1 mg
4 of drug, in the seventh hour 1.28 to 2.98 mg of drug, and in the eighth hour
5 0.76 mg to 1.76 mg of drug; (b) a dosage form exhibiting an ascending dose
6 profile in the first hour 0 mg to 3.00 mg, in the second hour 2.75 mg to 10 mg,
7 in the third hour 5 mg to 12 mg, in the fourth hour 5.5 mg to 13 mg, in the fifth
8 hour 6.15 mg to 14.5 mg, in the sixth hour 6.65 to 15.5 mg, in the seventh
9 hour 6.4 mg to 14.9 mg, and in the eighth hour 3.8 to 8.8 mg; (c) a dosage
10 form comprising a drug ascending release rate program of 0 mg to 0.400 mg
11 in the first hour, 0.376 mg to 1.81 mg in the second hour, 1.29 mg to 2.15 mg
12 in the third hour, 1.38 mg to 2.3 mg in the fourth hour, 1.54 mg to 2.57 mg in
13 the fifth hour, 1.66 mg to 2.76 mg in the sixth hour, 1.59 to 2.66 mg in the
14 seventh hour, and 0.93 to 1.58 mg in the eighth hour; and (d) a dosage form
15 that delivers an orally administrable drug in an ascending dose of 0 mg to
16 3.00 mg in the first hour, 2.45 mg to 9.05 mg in the second hour, 6.45 mg to
17 10.75 mg in the third hour, 6.9 mg to 11.5 mg in the fourth hour, 7.7 mg to
18 12.9 mg in the fifth hour, 8.3 mg to 13.8 mg in the sixth hour, 7.95 mg to
19 13.3 mg in the seventh hour, and 4.65 mg to 7.9 mg in the eighth hour.

20

21

EXAMPLES 20 TO 21

22

23 The procedures set forth in the above examples are followed with the
24 manufacture as described above, except in this invention, a first dosage form
25 is provided wherein the drug layer comprises 28 mg of methylphenidate
26 hydrochloride and a second dosage form is provided where the drug layer
27 comprises 42 mg of methylphenidate hydrochloride.

DISCLOSURE OF METHOD OF USING THE INVENTION

1
2
3 The invention pertains further to methods for delivering an ascending
4 dose over time to a warm-blooded animal in need of therapy. The invention
5 provides: (a) a method for delivering a dose of drug in an increasing rate to a
6 patient, wherein the method comprises administering orally to the patient a
7 drug in an increasing rate per hour over time, to provide the dose of drug to
8 the patient; (b) a method for delivering a dose of drug in an increasing dose
9 of drug to a patient, wherein the method comprises delivering orally to the
10 patient an orally administrable drug, in an increasing milligram dose per hour
11 over twenty-four hours, to deliver the dose of drug; (c) a method for delivering
12 a drug to a patient from a dosage form over time, wherein the method
13 comprises admitting orally into the patient a dosage form comprising
14 240 nanograms to 700 milligrams of drug that is delivered in an increasing
15 dose over time; and (d) a method comprising the steps of: (A) admitting into
16 a patient a dosage form comprising: (1) a wall that surrounds a compartment,
17 the wall comprising a semipermeable composition permeable to the passage
18 of fluid, including aqueous-biological fluid of the gastrointestinal tract, and
19 impermeable to the passage of drug; (2) a bilayer in the compartment
20 comprising a first layer comprising a dose of drug, a second layer comprising
21 an osmopolymer, or an osmopolymer and an osmagent, and for imbibing and
22 absorbing fluid for pushing the first layer from the dosage form and thereby
23 providing an increased dose per unit time over time; and (3) at least one exit
24 in the wall communicating with the first layer; (B) imbibing fluid through the
25 semipermeable wall at a rate determined by the permeability of the
26 semipermeable wall and the osmotic gradient across the semipermeable wall
27 causing the second layer to expand and swell; and (C) deliver the drug from
28 the first layer through the exit passageway to provide an ascending,
29 increasing dose of drug to the patient.

1 In summary, it will be appreciated the present invention contributes to
2 the art an unexpected dosage form that possesses the practical utility for
3 administering a sustained and increasing dose of drug at a dosage-metered
4 release rate over time. While the invention has been described and pointed
5 out in detail with reference to operative embodiments thereof, it will be
6 understood to those skilled in the art that various changes, modifications,
7 substitutions and omissions can be made without departing from the spirit of
8 the invention. It is intended, therefore, that the invention embraces those
9 equivalents within the scope of the claims.

1 We claim:

2

3 1. An osmotic tablet for administering a dose of drug to a patient,
4 wherein the osmotic tablet comprises:

5 (a) a drug composition comprising 10 ng to 700 mg of drug;
6 and

7 (b) an expandable composition comprising 100 ng to 400 mg
8 of a hydrophilic-expandable polymer; and wherein the drug composition and
9 the expandable composition are in contacting arrangement, and the osmotic
10 tablet administers the drug in an ascending-release rate to the patient.

11 2. The osmotic tablet for administering a dose of drug to a patient,
12 according to claim 1, wherein the drug is a member selected from the group
13 consisting of an opioid, barbiturate, hypnotic, central nervous system acting
14 drug, psychostimulant, psychodepressant, cannabinoid and catecholamine.

15 3. The osmotic tablet for administering a dose of drug to a patient
16 according to claim 1, wherein the drug is a member selected from the group
17 consisting of amphetamine, dextroamphetamine, methamphetamine,
18 methylphenidate, racemic methylphenidate, alkylphenidate, ethylphenidate,
19 ~~threomethylphenidate, phenylisopropylamine, and pemoline.~~

20 4. The osmotic tablet for administering a dose of drug to a patient
21 according to claim 1, wherein the drug is a pharmaceutically acceptable salt.

22 5. The osmotic tablet for administering a dose of drug to a patient
23 according to claim 1, wherein the osmotic tablet imbibes fluid from the patient
24 and administers the dose of drug.

25 6. An osmotic tablet for administering a dose of drug to a patient,
26 wherein the osmotic tablet comprises:

27 (a) a drug layer comprising 10 ng to 700 mg of drug; and,

28 (b) a osmotic layer comprising 80% to 95% of a composition
29 comprising an osmopolymer and an osmagent; and wherein the drug layer
30 and the osmotic layer comprise a bilayer that administers the drug in an
31 ascending-release rate to the patient.

1 7. The osmotic tablet for administering a dose of drug to a patient
2 according to claim 6, wherein the drug is a member selected from the group
3 consisting of an opioid, barbiturate, hypnotic, central nervous system acting
4 drug, psychostimulant, psychodepressant, cannabinoid, and catecholamine.

5 8. The osmotic tablet for administering a dose of drug to a patient
6 according to claim 6, wherein the drug comprises a member selected from the
7 group consisting of amphetamine, dextroamphetamine, methamphetamine,
8 alkylphenidate, methylphenidate, racemic methylphenidate, ethylphenidate,
9 threomethylphenidate, phenylisopropylamine, and pemoline.

10 9. The osmotic tablet for administering a drug to a patient
11 according to claim 6, wherein the drug is a pharmaceutically acceptable salt
12 selected from the group consisting of hydrochloride, hydrobromide, fumarate,
13 phosphate, sulfate, lactate, malate, acetate, tartrate, citrate, pamoate,
14 maleate, ascorbate, gluconate, aspartate and salicylate.

15 10. The osmotic tablet for administering a drug to a patient
16 according to claim 6, wherein the osmotic tablet an oral administration to the
17 patient imbibes fluid and administers the drug.

18 11. The osmotic tablet for administering a drug to a patient
19 according to claim 6, wherein a composition comprising a polymer envelops
20 the osmotic tablet.

21 12. The osmotic tablet for administering a drug to a patient
22 according to claim 6, wherein the osmotic tablet is longer than wide.

23 13. The osmotic tablet for administering a drug to a patient
24 according to claim 6, wherein the osmotic tablet is longer than thick.

25 14. A dosage form comprising:

- 26 (a) a first layer comprising 10 ng to 700 mg of drug;
27 (b) a second layer comprising 80% to 95% of a hydrophilic-
28 expandable polymer;
29 (c) a wall comprising a semipermeable composition that
30 surrounds the first and second layer;

1 (d) an exit in the wall communicating with the first layer for
2 delivering the drug; and wherein the dosage form when in operation
3 administers the drug in an ascending rate over time.

4 15. The dosage form according to claim 14, wherein the first layer
5 comprises a drug selected from the group consisting of an opioid, barbiturate,
6 hypnotic, central nervous system acting drug, psychostimulant,
7 psychodepressant, cannabinoid, and catecholamine.

8 16. The dosage form according to claim 14, wherein the first layer
9 comprises a drug selected from the group consisting of amphetamine,
10 dextroamphetamine, methamphetamine, methylphenidate, racemic
11 methylphenidate, alkylphenidate, ethylphenidate, threomethylphenidate,
12 phenylisopropylamine, and pemoline.

13 17. The dosage form according to claim 14, wherein the dosage
14 form comprises a length greater than its width and is designed for
15 administering the drug in an ascending-increasing dose over a sustained
16 time.

17 18. The dosage form according to claim 14, wherein the dosage
18 form comprises a length in excess of its width and the second layer
19 comprises 80% to 95% hydrophilic-expandable polymer that provides for an
20 ascending-increasing dose of drug over a sustained period.

21 19. The dosage form according to claim 1, wherein the first layer
22 comprises a poly(alkylene oxide) of 25,000 to 1,000,000 number-average
23 molecular weight.

24 20. The dosage form according to claim 14, wherein the first layer
25 comprises a carboxyvinylpolymer of 7,500 to 1,000,000 number-average
26 molecular weight.

27 21. The dosage form according to claim 14, wherein the first layer
28 comprises a carboxyalkylcellulose of 10,000 to 700,000 molecular weight.

29 22. The dosage form according to claim 14, wherein the second
30 layer comprises a poly(alkylene oxide) of 2,500,000 to 10,000,000 number-
31 average molecular weight.

1 23. The dosage form according to claim 14, wherein the second
2 layer comprises a carboxyalkylcellulose of 1,750,000 to 10,000,000 number-
3 average molecular weight.

4 24. The dosage form according to claim 14, wherein the first and
5 second layers comprise a hydroxypropylalkylcellulose.

6 25. The dosage form according to claim 14, wherein the first and
7 second layers comprise a hydroxyalkylcellulose.

8 26. A dosage form comprising:

9 (a) a first layer comprising 10 ng to 700 mg of drug;

10 (b) a second layer comprising a composition comprising
11 80% to 95% of an osmopolymer and an osmagent;

12 (c) a wall comprising a semipermeable composition that
13 surrounds the first and second layers;

14 (d) an exit in the wall communicating with the first layer for
15 delivering the drug; and wherein the dosage form when in operation
16 administers the drug in an increasing sustained dose over time.

17 27. The dosage form according to claim 24, wherein an overcoat
18 comprising a drug is on the exterior surface of the wall.

19 28. The dosage form according to claim 24, wherein the first layer
20 comprises a drug selected from the group consisting of amphetamine,
21 dextroamphetamine, methamphetamine, methylphenidate, racemic
22 methylphenidate, alkylphenidate, ethylphenidate, threomethylphenidate,
23 phenylisopropylamine, and pemoline.

24 29. The dosage form according to claim 24, wherein the dosage
25 form comprises a length in excess of its width.

26 30. The dosage form according to claim 24, wherein the dosage
27 form comprises a length in excess of its thickness.

28 31. The dosage form according to claim 24, wherein the second
29 layer composition comprising the osmopolymer and the osmagent combine
30 with the dosage form design to deliver the drug in an increasing sustained
31 dose over time.

1 32. The dosage form according to claim 24, wherein the first and
2 second layers comprise a poly(alkylene oxide) and the poly(alkylene oxide) in
3 the second layer has a higher number-average molecular weight.

4 33. The dosage form according to claim 24, wherein the first and
5 second layers comprise a carboxyalkylcellulose and the carboxyalkylcellulose
6 in the second layer comprises a higher molecular weight.

7 34. The dosage form according to claim 24, wherein the first and
8 second layers comprise a hydroxypropylalkylcellulose.

9 35. The dosage form according to claim 24, wherein the first and
10 second layers comprise a hydroxyalkylcellulose.
11 in an increasing dose over time, wherein the method comprises admitting
12 orally into the patient a dosage form comprising 240 nanograms to 700
13 milligrams of drug that delivers the drug in an increasing dose per hour over
14 time to deliver the dose of drug to the patient.

1 / 3

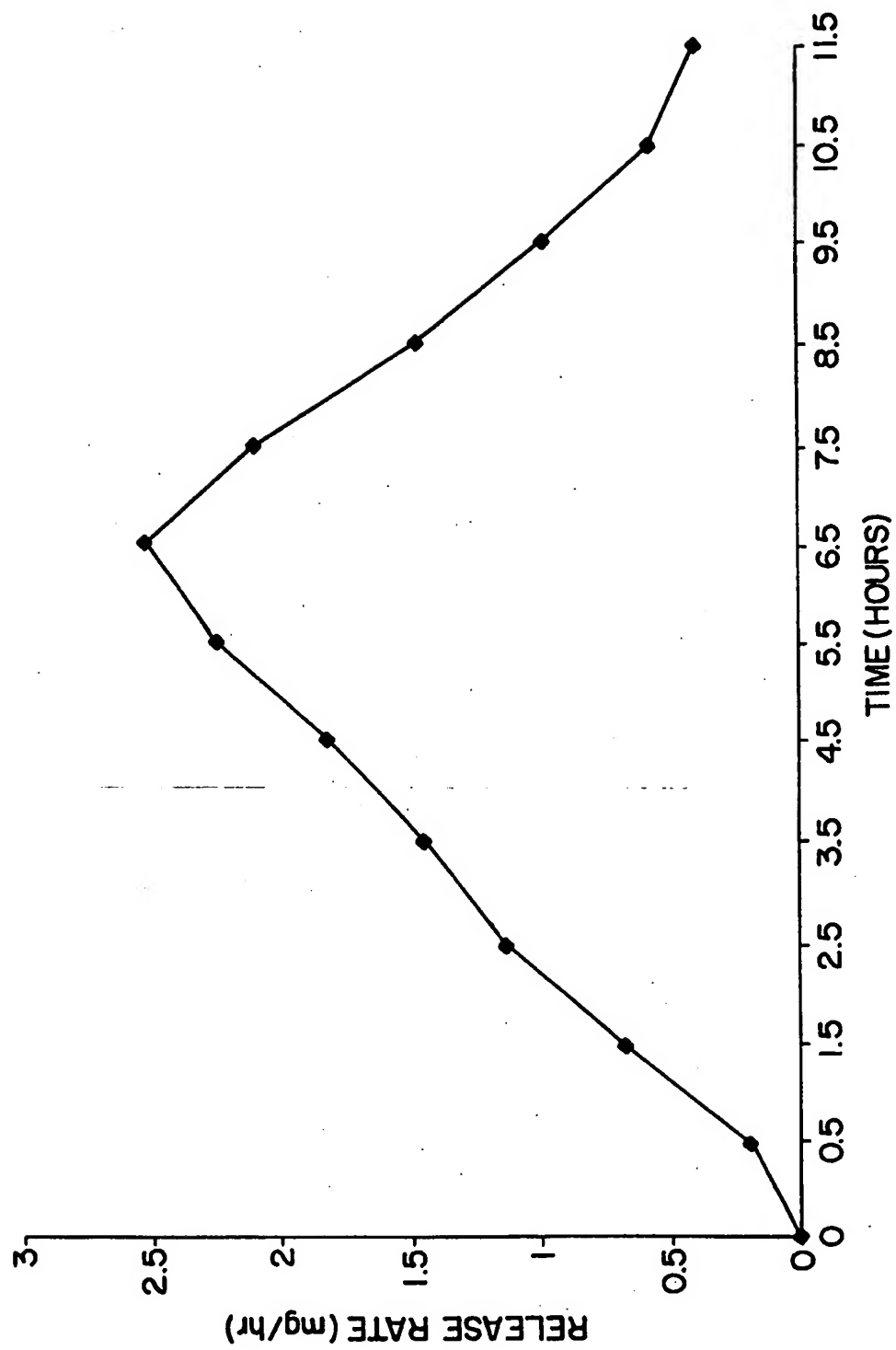


FIG. 1

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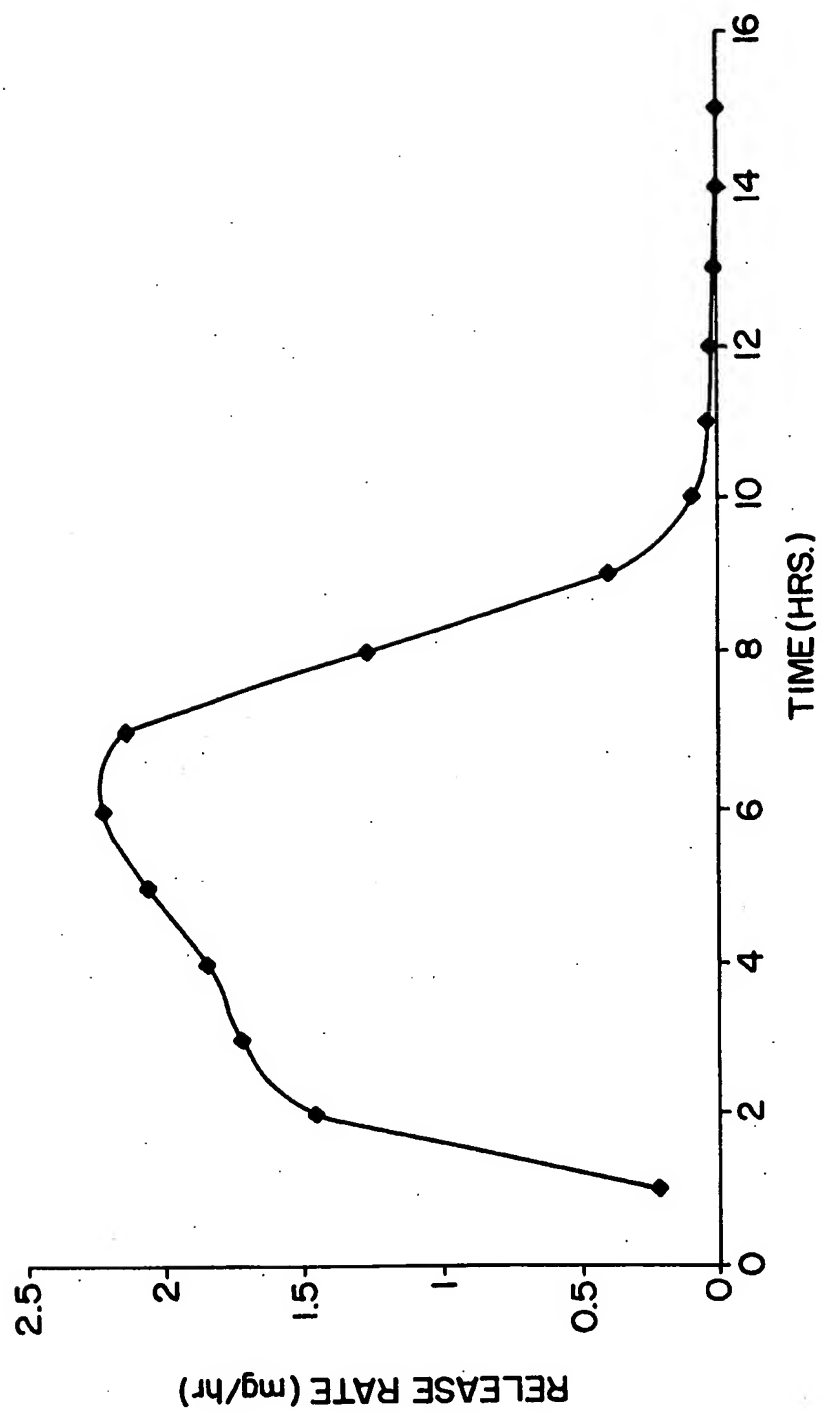
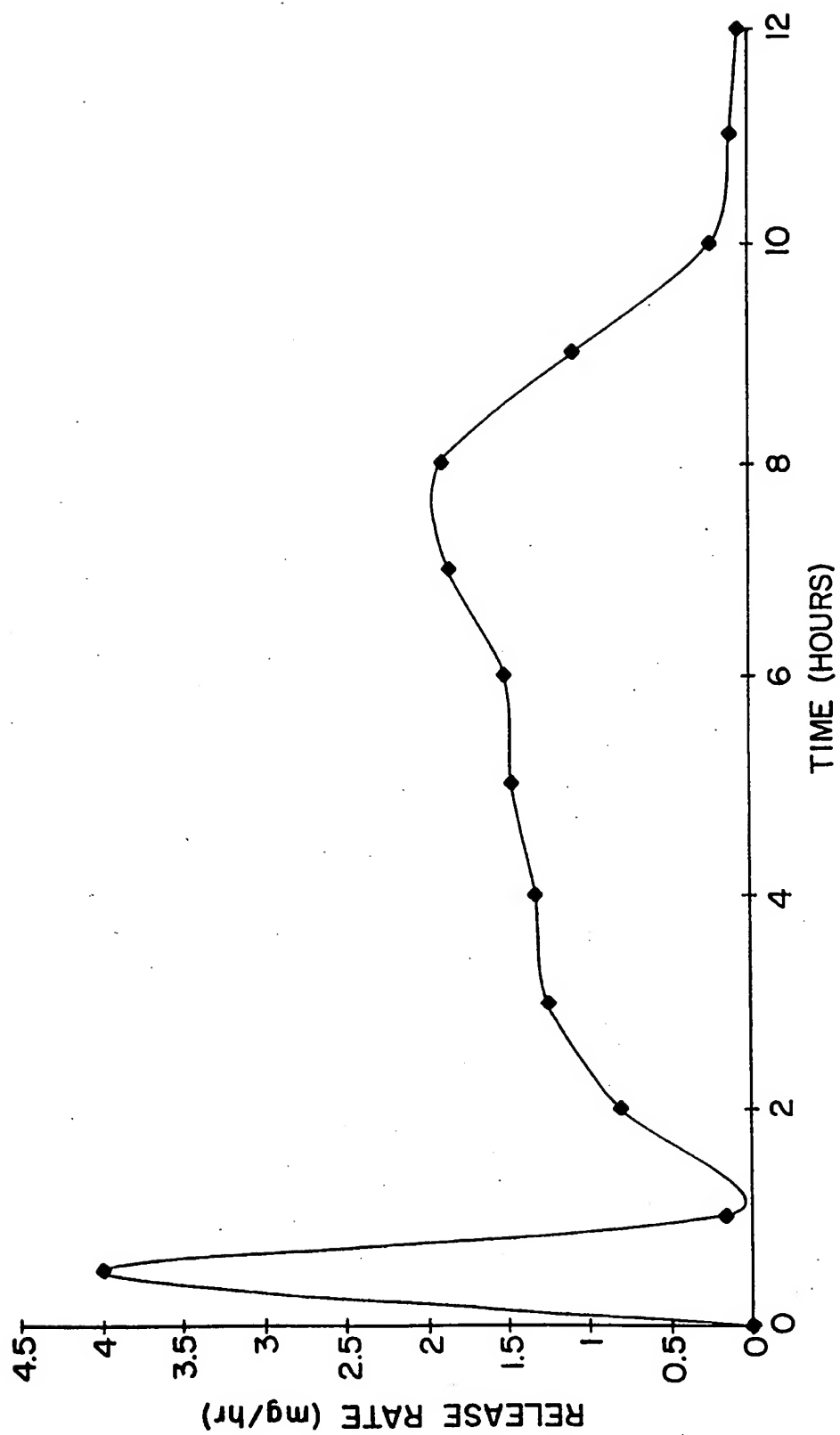


FIG. 2

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 97/22016

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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| X | WO 91 03247 A (ALZA CORP) 21 March 1991 see page 10 - page 12; example 2 --- | 1,5-14, 19,22, 24,26, 31,32,34 |
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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